09/828241

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Term: L1 and ((plurality near5 muta$5) or (multiplex near5 muta$5))

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L3	L2 and label$1	1	L3
L2	L1 and ((plurality near5 muta$5) or (multiplex near5 muta$5))	2	L2
L1	ion pairing near5 reverse phase$1	24	L1

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L3: Entry 1 of 1 File: USPT Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6210885 B1
TITLE: Modifying double stranded DNA to enhance separations by matched ion polynucleotide chromatography

Brief Summary Text (20):
Recently, an ion pairing reverse phase HPLC method was introduced to effectively separate mixtures of double stranded polynucleotides, in general and DNA, in particular, wherein the separations are based on base pair length. This method is described in the following references which are incorporated herein in their entireties: U.S. Pat. No. 5,795,976 (1998) to Oefner; U.S. Pat. No. 5,585,236 (1996) to Bonn; Huber, et al., Chromatographia 37:653 (1993); Huber, et al., Anal. Biochem. 212:351 (1993).

Brief Summary Text (26):
The use of radioactive labels is a well known method of detection in the DNA separation art. However, this method is costly, developing autoradiograms to visualize a separation is a very lengthy process, and radioactivity poses a health hazard.

Drawing Description Text (17):
FIG. 16 shows a multiplex DMIPC chromatogram of a 209 bp mutation standard tagged with FAM and JOE.

Detailed Description Text (61):
As defined herein, a "chemical tag" is a molecule which can be covalently bound to a polynucleotide for the purpose of increasing the sensitivity of detection of the polynucleotide (e.g., a label) and/or increasing the retention time of the polynucleotide during separation by MIPC.

Detailed Description Text (67):
The use of fluorescent tags to enhance the detection of DNA fragments separated by liquid chromatography has been described in the following references which are incorporated in their entireties herein: Oefner, et al. Research Reports 16:898 (1994) and Oefner, et al., Anal. Biochem., 223:1 (1994). Morgan, et al., (J. Chromatography 536:84 (1991)) found that fluoroscein and biotin tagged DNA fragments could not be completely eluted from a porous alkylated polystyrene HPLC column. Changing the column packing to other porous polymers improved the elution behavior of the tagged DNA, but not their resolution. Further advances were made by Oefner and co-workers in the use of fluorescent labels to enhance the detection sensitivity in oligonucleotides and double stranded DNA separations by HPLC on non-polar stationary phases. Oefner, et al., (Analytical Biochemistry 223:1 (1994)) describe the use of fluorescent dyes to covalently label double stranded nucleic acids which were separated by HPLC. They report an increase in sensitivity of 167-1000-fold compared to uv absorbance detection. However, their separation system did not include precautions against contamination of the media or chromatographic system by multivalent cations, which precautions have been shown by Applicants to essentially eliminate the degradation in separation performance.

Detailed Description Text (69):
In one embodiment of the invention, the fluorescent dyes can be covalently bonded to the DNA fragments. In another embodiment, the dyes can be bound by reversible interactions (such as by intercalation or by binding into a DNA groove). In either case the fluorescent dye greatly enhances the sensitivity of detection of the DNA fragment compared to uv detection. The use of fluorescent dyes to enhance the detection sensitivity of DNA fragments separated by MIPC or DMIPC has not been

previously disclosed. Fluorescent tags provide a label for detection (this will be discussed hereinbelow) and enhance detection relative to uv. Thus, they are very useful when limited amounts of sample are available for analysis. The only requirement for tagging DNA with intercalating fluorescent dyes is that the intercalated complex be stable under MIPC and DMIPC conditions, i.e., between about 50.degree. C. and 70.degree. C., preferably, between 50.degree. C. and 60.degree. C.

Detailed Description Text (78):
FIGS. 14, 15, and 16 illustrate a multiplex DMIPC analysis of a 209 bp mutation standard tagged with FAM (520 nm) and JOE (548 nm). The pooled samples were analyzed on an MIPC column under partially denaturing conditions, 56.degree. C., and the chromatography was monitored at 520 nm and 548 nm simultaneously. The chromatogram shown in FIG. 14 was monitored at 520 nm (exited at 496 nm). The chromatogram in FIG. 15 was monitored at 548 nm (exited at 520 nm). The chromatogram in FIG. 16 shows the chromatograms from FIGS. 14 and 15 superimposed for comparison. As can be seen in FIG. 16, the two samples are clearly distinguishable. For example, at 5 minutes retention time, the JOE tagged standard shows a strong peak while the FAM tagged standard shows essentially no response. At about 4.6 minutes retention time, the FAM tagged standard shows a peak while the JOE tagged standard shows a trough.

Other Reference Publication (24):
Shi et al. Synthesis, Characterization and Luminescent Properties of EU111 and TB111 Fluorescent Chelated Used as Label in Medical Immunoassays, Journal of Alloys an Compounds, 207/208, pp. 29-32 1994.

☐ Generate Collection

L2: Entry 1 of 2 File: USPT Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6461819 B1
TITLE: Analysis of nicked DNA by matched ion polynucleotide chromatography under denaturing conditions

Detailed Description Text (3):
Ion Pairing Reverse Phase HPLC (IPRPHPLC) effectively separates mixtures of double stranded polynucleotides, in general and DNA, in particular, wherein the separations are based on base pair length (U.S. Pat. No. 5,585,236 to Bonn (1996)). IPRPHPLC is not limited by any of the deficiencies associated with gel based separation methods.

Other Reference Publication (21):
Rowley et al., Ultrarapid Mutation Detection by Multiplex, Solid-Phase Chemical Cleavage, Genomics, 30, 574-582, 1995.

CLAIMS:

3. A method for determining the presence of a nick in a known fragment of double stranded DNA comprising: (a) applying said fragment to a reverse phase separation column; (b) eluting said fragment under denaturing conditions by Ion Pairing Reverse Phase HPLC; (c) detecting the single stranded DNA species eluted in step (b); and (d) quantifying the single stranded DNA species from step (c) wherein at least three single stranded DNA species are detected if said fragment has a nick.

09/828,211

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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=> s ion pairing(10a)reverse phase#
L1          298 ION PAIRING(10A) REVERSE PHASE#

=> s l1 and ((multip###(10a) muta#####) or (plurality(10a)muta#####))
L2            0 L1 AND ((MULTIP###(10A) MUTA#####) OR (PLURALITY(10A) MUTA#####)
                )

=> s l1 and (multipl###(10a)(delet### or insert###))
L3            0 L1 AND (MULTIPL###(10A)(DELET### OR INSERT###))

=> s l2 and multip### and muta#####
L4            0 L2 AND MULTIP### AND MUTA#####

=> s l1 and mutat#####
L5            8 L1 AND MUTAT#####

=> s l5 and (multipl### or pluralit###)
L6            0 L5 AND (MULTIPL### OR PLURALIT###)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L7            3 DUP REM L5 (5 DUPLICATES REMOVED)

=> d l7 1-3 bib ab kwic

L7   ANSWER 1 OF 3     MEDLINE                              DUPLICATE 1
AN   2002199471     MEDLINE
DN   21929802   PubMed ID: 11933191
TI   DHPLC screening of cystic fibrosis gene mutations.
AU   Ravnik-Glavac Metka; Atkinson Andrew; Glavac Damjan; Dean Michael
CS   Human Genetics Section, Laboratory of Genomic Diversity, National Cancer
     Institute at Frederick, Frederick, Maryland, USA.
SO   HUMAN MUTATION, (2002 Apr) 19 (4) 374-83.
     Journal code: 9215429. ISSN: 1098-1004.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200208
ED   Entered STN: 20020405
     Last Updated on STN: 20020831
     Entered Medline: 20020830
```

AB Denaturing high performance liquid chromatography (DHPLC) using **ion-pairing reverse phase** chromatography (IPRPC) columns is a technique for the screening of gene **mutations**. In order to evaluate the potential utility of this assay method in a clinical laboratory setting, we subjected the PCR products of 73 CF patients known to bear CFTR **mutations** to this analytic technique. We used thermal denaturation profile parameters specified by the MELT program tool, made available by Stanford University. Using this strategy, we determined an initial analytic sensitivity of 90.4% for any of 73 known CFTR **mutations**. Most of the **mutations** not detected by DHPLC under these conditions are alpha-substitutions. This information may eventually help to improve the MELT algorithm. Increasing column denaturation temperatures for one or two degrees above those recommended by the MELT program allowed 100% detection of CFTR **mutations** tested. By comparing DHPLC methodology used in this study with the recently reported study based on Wavemaker 3.4.4 software (Transgenomic, Omaha, NE) [Le Marechal et al., 2001) and with previous SSCP analysis of CFTR **mutations** [Ravnik-Glavac et al., 1994] we emphasized differences and similarities in order to refine the DHPLC system and discuss the relationship to the alternative approaches. We conclude that the DHPLC method, under optimized conditions, is highly accurate, rapid, and efficient in detecting **mutations** in the CFTR gene and may find high utility in screening individuals for CFTR **mutations**. Hum **Mutat** 19:374-383, 2002. Published 2002 Wiley-Liss, Inc.

TI DHPLC screening of cystic fibrosis gene **mutations**.

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CT . . . Tags: Human
Algorithms
*Chromatography, High Pressure Liquid: MT, methods
*Cystic Fibrosis: GE, genetics
*Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics
***DNA Mutational Analysis: MT, methods**
Exons: GE, genetics
*Genetic Screening: MT, methods
***Mutation: GE, genetics**
Nucleic Acid Denaturation
Polymorphism, Single-Stranded Conformational
Sensitivity and Specificity
Software

Temperature
Time Factors

L7 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1987:186383 BIOSIS
DN BA83:94507
TI A DYNAMIC STUDY ON THE VARIATION OF BIOSYNTHESIZED COMPONENTS OF THE CEPHALOSPORIN C PRODUCER CEPHALOSPORIUM-ACREMONIUM.
AU XU X-Y; ZHAO C-Y
CS INST. ANTIBIOTICS, CHINESE ACADEMY MED. SCI., BEIJING, CHINA.
SO CHIN J ANTIBIOT, (1986 (RECD 1987)) 11 (6), 468-473.
CODEN: KANGDS. ISSN: 0254-6116.
FS BA; OLD
LA Chinese
AB The present communication is concerned with the variation of three biosynthesized components-cephalosporin C, deacetylcephalosporin C and deacetoxycephalosporin C by the different Cephalos porium acremonnium mutants. The fermentation period of six mutants (M1, M2, M3, M4, M5 and M6) have been entirely analyzed on the **reverse phase** High Performance Liquid Chromatography with **ion-pairing** techniques. The data was studied that the variation between three components was dynamical. In compared with six mutants, after **mutation**, one of them (M6) was not only increased its antibiotic production but also stabilized the percentage of the desired component.
AB. . . mutants. The fermentation period of six mutants (M1, M2, M3, M4, M5 and M6) have been entirely analyzed on the **reverse phase** High Performance Liquid Chromatography with **ion-pairing** techniques. The data was studied that the variation between three components was dynamical. In compared with six mutants, after **mutation**, one of them (M6) was not only increased its antibiotic production but also stabilized the percentage of the desired component.

L7 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
AN 1982:525583 CAPLUS
DN 97:125583
TI Detection of an altered I-A .beta. polypeptide in the murine Ir mutant, B6.C-H-2bm12
AU Lee, David R.; Hansen, Ted. H.; Cullen, Susan E.
CS Sch. Med., Washington Univ., St. Louis, MO, 63110, USA
SO Journal of Immunology (1982), 129(1), 245-51
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
AB A spontaneous mutant mouse strain, B6.C-H-2bm12 (bm12), isolated on the basis of reciprocal skin graft rejection with the parental strain, B6, was examd. Genetic anal. of bm12 mice had localized the **mutation** to the 1-A subregion of the murine major histocompatibility complex (MHC). Alterations in the serol. determinants, lymphocyte-activating determinants (LAD), and immune response characteristics assocd. with I-A mols. have been noted in bm12 mice. The structural characterization of the 1-A mols. from mutant and parental mice was undertaken. Spleen cell I-A antigens from the mutant, bm12, and the parent, B6, were radiolabeled and isolated using alloantisera. The .alpha.- and .beta.-chains were sepd. by SDS-polyacrylamide electrophoresis and compared by **ion-pairing reverse phase** high-performance liq. chromatog. of tryptic (T) and tryptic-insol. chymotryptic (TIC) peptides. The T and TIC peptide maps of the [3H]Arg-, [3H]Lys-, or [3H]Leu-labeled .alpha.-chains showed no differences between mutant and parent. In contrast, the T peptide maps of the [3H]Arg- or [3H]Leu-labeled .beta.-chains revealed 2 unique B6 T peptides and 2 unique bm12 T peptides. The T peptide comparison of [3H]Lys-labeled .beta.-chain revealed a unique bm12 T peptide. Anal. of the [3H]mannose-labeled .beta.-chains by T and TIC peptide mapping indicated that the peptide shifts obsd. using different [3H]amino acids were not due to differences

in N-linked glycosylation, but probably to differences in the polypeptide structure. Thus the bm12 and B6 1-A .alpha.-chains are probably identical, and the Ir alteration in bm12 mice may result from an 1-A .beta.-chain that is altered at a min. of 3 different sites in the polypeptide backbone. The possibility that independent functional domains exist on 1-A mols. is raised.

AB A spontaneous mutant mouse strain, B6.C-H-2bm12 (bm12), isolated on the basis of reciprocal skin graft rejection with the parental strain, B6, was examd. Genetic anal. of bm12 mice had localized the **mutation** to the 1-A subregion of the murine major histocompatibility complex (MHC). Alterations in the serol. determinants, lymphocyte-activating determinants (LAD), and immune response characteristics assocd. with I-A mols. have been noted in bm12 mice. The structural characterization of the 1-A mols. from mutant and parental mice was undertaken. Spleen cell I-A antigens from the mutant, bm12, and the parent, B6, were radiolabeled and isolated using alloantisera. The .alpha.- and .beta.-chains were sepd. by SDS-polyacrylamide electrophoresis and compared by **ion-pairing reverse phase** high-performance liq. chromatog. of tryptic (T) and tryptic-insol. chymotryptic (TIC) peptides. The T and TIC peptide maps of the [3H]Arg-, [3H]Lys-, or [3H]Leu-labeled .alpha.-chains showed no differences between mutant and parent. In contrast, the T peptide maps of the [3H]Arg- or [3H]Leu-labeled .beta.-chains revealed 2 unique B6 T peptides and 2 unique bm12 T peptides. The T peptide comparison of [3H]Lys-labeled .beta.-chain revealed a unique bm12 T peptide. Anal. of the [3H]mannose-labeled .beta.-chains by T and TIC peptide mapping indicated that the peptide shifts obsd. using different [3H]amino acids were not due to differences in N-linked glycosylation, but probably to differences in the polypeptide structure. Thus the bm12 and B6 1-A .alpha.-chains are probably identical, and the Ir alteration in bm12 mice may result from an 1-A .beta.-chain that is altered at a min. of 3 different sites in the polypeptide backbone. The possibility that independent functional domains exist on 1-A mols. is raised.

=>